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Therapeutic Class Review
Monoamine Oxidase-B Inhibitors

Overview/Summary

Parkinson's disease is a progressive neurodegenerative motor system disorder in which the cardinal features consists of tremor, bradykinesia and rigidity. The incidence and prevalence of Parkinson's disease increases with age and its impact is set to increase as the population ages.[1] Monoamine oxidase-B Inhibitors (MAO-B) are one of several pharmacologic options used for the management of the symptoms associated with Parkinson's disease and major depressive disorder.

Currently there are two irreversible MAO-B inhibitors available in the United States, selegiline (Eldepryl®, EMSAM® and Zelapar®) and rasagiline (Azilect®).[2-3] The oral dosage formulations of selegiline are Food and Drug Administration (FDA) approved for combination therapy with levodopa for the treatment of the signs and symptoms of Parkinson's disease. Additionally, the transdermal dosage form is FDA approved for major depressive disorder. Rasagiline is FDA approved for monotherapy treatment of the signs and symptoms of Parkinson's disease.

Selegiline is available in tablet, capsule, orally disintegrating tablet (ODT), and transdermal patch (indicated for depression only) formulations.[2,3] At low doses it is selective for MAO-B and non-selective at high doses. In addition, at low doses selegiline modulates dopaminergic neurotransmission and increases serotonin (5-HT), noradrenergic, and dopaminergic neurotransmission at high doses. Selegiline treats Parkinson's disease at low doses, due to its selectivity to MAO-B and ability to modulate dopamine.[1-4] The transdermal formulation of selegiline (EMSAM®) is not FDA approved for the treatment of Parkinson's disease.[4] Selegiline is currently available generically in tablet and capsule form however, Zelapar®, an orally disintegrating tablet, and EMSAM® a transdermal patch are not available generically.

Rasagiline (Azilect®) irreversibly inhibits MAO-B, and is available as a tablet. The pharmacokinetic profile of rasagiline indicates a very short half-life of 45 minutes, extensive tissue distribution, and metabolism by the hepatic CYP1A2 isoenzyme pathway.[5-7] Comparative trials with selegiline and other Parkinson's disease agents (i.e., dopamine agonists) are lacking, and it remains unclear whether rasagiline offers any clinical advantage over selegiline or other antiparkinson's disease agent.

An overview of the currently available Parkinson's disease guidelines indicates that there is no overall agreement between the guidelines as to which is the preferred agent for initial treatment. However, the guidelines agree that levodopa produces the most efficacious relief of Parkinson's symptoms. The National Institute for Health and Clinical Excellence (NICE), the American Academy of Neurology (AAN) and the European Federation of Neurological Societies/Movement Disorder Society, suggest that MAO-B inhibitors provide mild to modest symptomatic relief of Parkinson's disease compared to levodopa and dopamine agonists.[8-12]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Rasagiline (Azilect®)	Monoamine Oxidase-B Inhibitor	-
Selegiline (Eldepryl®, EMSAM®, Zelapar®)	Monoamine Oxidase-B Inhibitor	✔ *

*EMSAM® transdermal patch and Zelapar® oral disintegrating tablets are not available generically.

Indications

Table 2. Food and Drug Administration Approved Indications[2-7]

Generic Name	Monotherapy for the Treatment of the Sign and Symptoms of Parkinson's Disease	Combination Therapy with Levodopa for the Treatment of the Sign and Symptoms of Parkinson's Disease	Major Depressive Disorder
Rasagiline	✔	✔	
Selegiline		✔ (all oral agents)	✔ (transdermal patch)

In addition to its Food and Drug Administration (FDA) approved indications, selegiline oral agents may also be used off-label for depression, tardive dyskinesia, attention-deficit/hyperactivity disorder, negative symptoms of schizophrenia, Alzheimer's disease dementia, periodic leg movement and narcolepsy.

Pharmacokinetics

Table 3. Pharmacokinetics[2-7]

Generic Name	Bioavailability (%)	Metabolism	Renal Excretion (%)	Active Metabolites	Half-Life (hours)
Rasagiline	36	Hepatic (near complete)	62	1(R)-aminoindan, 3 - hydroxy-N-propargyl-1 aminoindan, 3-hydroxyl-1-aminoindan	3
Selegiline	Oral tablet and capsule: not reported; (increased 3 to 4 fold when taken with food) Oral disintegrating tablets: % not reported, greater than capsule/tablet Transdermal patch: 10-40	Hepatic (extensive)	Not reported	N-desmethylselegiline, L-amphetamine, L-methamphetamine	10 (oral agents) 18-25 (transdermal patch)

Clinical Trials

A meta-analysis conducted by Macleod et al, evaluated the safety and long-term efficacy of Monoamine oxidase-B (MAO-B) inhibitors in patients with early Parkinson's disease. In total 2,422 patients in 10 randomized placebo-controlled trials were evaluated. The primary endpoints were the number of deaths at the end of follow-up, disease progression, levodopa requirement, time to levodopa introduction and motor fluctuations associated with Parkinson's disease treatment. Death at the end of follow-up was non-significant among those that received MAO-B inhibitors compared to control (P=0.21). Slower disease progression favored MAO-B inhibitors, particularly in improving activities of daily living, conducted by the Unified Parkinson's Disease Rating Scale for Activity of Daily Living (UPDRS-ADL) (P=0.004). Treatment with MAO-B inhibitors delayed the requirement of levodopa compared to control. The median time of

levodopa introduction was delayed in patients on MAO-B inhibitors (4.1 to 8.7 months). However, conclusions to the time to levodopa treatment in levodopa naïve patients could not be made. Additionally, delaying the development of motor complications significantly favored the MAO-B inhibitors compared to control (*P*=0.01). In terms of safety, patients treated with MAO-B inhibitors had a non-significant trend towards the development of an adverse event compared to control. The overall number of withdrawals were not reported, however patients treated with MAO-B inhibitors had more withdrawals compared to the control group in 6 trials evaluating 1,226 patients.[1]

A study conducted with selegiline orally disintegrating tablets (ODT) by Ondo et al, evaluated the reduction in the total average daily off time at weeks 10 and 12, in which the results were not statistically significant compared to placebo. Selegiline ODT did demonstrate significant dyskinesia free on-time at 12 weeks, with an increase from 8.4 to 10.3 hours daily compared to placebo, which had an increase from 8.8 to 9.7 hours daily (*P*=0.035).[13]

In rasalagine efficacy trials, all primary endpoints determined that rasagiline significantly reduced mean total daily off time and improved UPDRS scores over placebo.[14-16]

Safety was evaluated in a trial of 56 patients diagnosed with idiopathic Parkinson's disease taking rasalagine. No serious adverse events were reported in the treatment groups and the frequency of adverse events was similar to those reported by patients receiving placebo.[17]

Selegiline transdermal patch is Food and Drug Administration (FDA) approved for major depressive disorder, but not Parkinson's disease. This approval was based on three randomized placebo-controlled trials. In all three trials, a majority of the primary outcomes demonstrated a significant improvement in depression rating scores compared to placebo.[18-21]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Parkinson's Disease				
Macleod et al[1] Selegiline or rasagiline or lazabemide vs placebo, levodopa or dopamine agonist	MA Randomized clinical trials comparing MAO-B inhibitors with a control intervention in early Parkinson's disease, studies included recruited patients with a clinical diagnosis of idiopathic Parkinson's disease who have not started treatment or had started treatment within 12 months and had a Hoehn and Yahr Stage-II or less	N=2,422 (10 studies) 1 to 9.2 years Mean duration=5.8 years	Primary: Effectiveness evaluated by: number of patients who were either dead or disabled from any cause at end of follow-up, the number of deaths that occurred, disease progression in terms of severity of impairment, disability and quality of life which were measured by scales (UPDRS and UPDRS ADL), levodopa requirement, mean levodopa dose, the number of patients requiring levodopa, time to the introduction of levodopa or a dopamine agonist, number of patients with motor fluctuations, number of patients with dyskinesias, safety (number of	Primary: All the studies were evaluated, they all reported data on death at the end of follow-up. Data was available for 2,389 patients (98.7% of all patients). Overall there was a non-significant increase in deaths amongst patients treated with MAO-B inhibitors compared with those given control (OR, 1.16; 95% CI, 0.92 to 1.44; *P*=0.21). UPDRS motor scores at one year follow up were reported from two studies (217 patients, 9% of all patients), in which both studies favored treatment with MAO-B inhibitors (*P* value not reported). Mean change in UPDRS-ADL score from baseline to endpoint were reported from six studies (1,262 patients, 52% of all patients, 88% randomized in the six studies), and favored treatment with MAO-B inhibitors (95% CI, -2.53 to -0.48; *P*=0.004). Participants requiring levodopa were reported from three studies (1,088 patients, 77% without levodopa at the beginning), and favored treatment with MAO-B inhibitors (OR, 0.53; 95% CI, 0.36 to 0.79; *P*=0.01). The absolute rate of requiring levodopa at one year varied in the control groups of the three trials from 15% to 60%. Time until levodopa was required was reported from five studies (1,288 patients, 91% of patients in trials without levodopa from the outset), however the data from these studies was skewed and it was not possible to use formal meta-analysis. However, the data from these studies showed a delay in the median time to introduce levodopa with MAO-B inhibitor treatment between 4.1 and 8.7 months. Mean levodopa dose data was reported from five clinical trials. Meta-analysis could not be conducted because the data was skewed with substantial heterogeneity. All the studies showed higher levodopa doses in the control groups compared to the patients treated with MAO-B inhibitors. The difference in levodopa dose varied from 30 to 185 mg/day and generally increased as the duration of follow-up increased. Motor fluctuations data was reported from five clinical trials (1,319 patients, 54% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			patients with adverse events, number of withdrawals due to adverse events and total number of withdrawals) Secondary: Not reported	all patients, 80% of those randomized in the five clinical trials). Delaying the development of motor complications significantly favored the MAO-B inhibitors. (OR, 0.75; 95% CI, 0.59 to 0.94; *P*=0.01). In addition, there was no difference between the high-quality trials and the low quality trials (*P*=0.78) and there was no difference between the trials that used levodopa at the beginning and the trials that used MAO-B inhibitors alone from onset (*P*=0.29). Dyskinesia data was reported from four studies (1,228 patients, 51% of all patients, 80% of those randomized in the four trials). The results demonstrated no difference between the intervention group and the control group. Four clinical trials (614 patients, 26% of all patients, 97% of those randomized in the four clinical trials) reported the number of patients with any serious adverse event. Overall, there was a non-significant trend for more adverse events with the MAO-B inhibitors (OR, 1.38; 95% CI, 0.92 to 2.06; *P*=0.12). In five studies (1,203 patients, 50% of all patients), patients treated with MAO-B inhibitors reported the occurrence of nausea more than patients treated with the control did. However, the overall difference compared to the control group was non-significant (*P* value not reported). Six trials (1,226 patients, 51% of all patients) reported the number of withdrawals due to an adverse event at the end of follow-up. There were significantly more withdrawals with the MAO-B inhibitors compared to the control group (OR, 2.36; 95% CI, 1.32 to 4.20; *P*=0.004). The rate of withdrawal in the control group was about 10% implying that every ten patients treated there would be one expected withdrawal for a patient treated with an MAO-B inhibitor. There were no significant differences between high and low quality studies (*P*=0.47) and trials that initiated levodopa or dopamine agonist from the beginning (*P* value not reported) and trials which initiated MAO-B inhibitors alone from the outset (*P*=0.70). The total number of withdrawals was not reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ondo et al[13] Selegiline ODT 1.25 mg increased to 2.5 mg daily vs placebo	DB, PC, RCT Patients ≥30 years of age with a confirmed diagnosis of idiopathic Parkinson's disease with a documented response to levodopa along with symptoms of deterioration at the end of the levodopa dosing interval, must have predictable mild to moderate motor fluctuation associated with 3 hours of off-time daily	N=150 Selegiline ODT=100 Placebo=50 12 weeks	Primary: Reduction in total daily off as determined by the average of the percentages of off-time reported at weeks 10 and 12 Secondary: Reduction in hours off, changes from baseline to the study endpoint in the motor (off and on) and ADL subscales of the UPDRS, CGI-I, CGI-S and PGI-I scales	Primary: At weeks 10 and 12 (2.5 mg), the average daily off-time was reduced by 11.6%±17.5% in the selegiline ODT group versus 9.8%±14.9% in the placebo group (*P*=0.467), which is not statistically significant. The average number of daily off-hours was 0.3 hours greater in the selegiline ODT group than in the placebo group (*P*=0.588), also not demonstrating statistical significance. The on time without dyskinesia at combined weeks 10 and 12 was not different from control. However, dyskinesia free on-time at 12 weeks was significantly superior with selegiline ODT, with an increase from 8.4 to 10.3 hours daily compared to placebo which had an increase from 8.8 to 9.7 hours daily (*P*=0.035). Secondary: No significant differences were observed between selegiline ODT and placebo in the UPDRS motor and ADL scores (*P* value not reported). Selegiline ODT significantly improved PGI-I scores (*P*=0.020) but did not improve CGI-I scores (*P*=0.64) compared to placebo. Selegiline ODT was well tolerated. The discontinuation due to an adverse event occurred in seven patients in the selegiline ODT group and zero patients in the placebo group. Those seven patients that discontinued were due to accidental injury, depression, skin disorder, chest pain, myasthenia, tremor, dizziness and dyskinesia. Blood pressure assessments were similar in both groups at final evaluation.
Rascol et al[14] (LARGO) Rasagiline 1 mg daily vs entacapone 200 mg with every levodopa dose	DB, DD, PC, PG, RCT Patients with a confirmed diagnosis of idiopathic Parkinson's disease who were in a modified Hoehn and Yahr	N=687 18 weeks	Primary: The change from baseline to week 18 in mean total daily off-time as measured by 24-hour diaries Secondary: Change from baseline to end of	Primary: Both rasagiline and entacapone reduced mean total daily off-time from baseline by more than 1-hour, and almost three times more than the reduction with placebo (*P*=0.0001 and *P*<0.0001, respectively). This effect was evident at the first efficacy assessment at week 6, mean change -1.31 for rasagiline and -1.06 for entacapone vs -0.27 for placebo (*P*<0.0001 and *P*=0.0006, respectively). Secondary: At week 18 the CGI-I score improved compared to placebo by 0.49 units for rasagiline and 0.36 units (*P*<0.0001) for entacapone (*P*=0.0002) from baseline.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	stage of less than 5 in the off state and experience at least 2 ½ hours in the off state daily confirmed by a baseline 3-day diary		treatment of CGI-I during on-time measured by examiner, UPDRS-ADL scores during off-time and UPSRD-motor examination scores during on-time	Compared to placebo the UPDRS-motor score (on state) for rasagiline improved by -2.94 (*P*<0.0001) and -2.73 for entacapone (*P*<0.0001). The UPDRS-ADL score improved by -1.71 for rasagiline (*P*<0.0001) and by -1.38 for entacapone (*P*=0.0006) compared to placebo. There were three UPDRS exploratory subscales conducted during the trial measuring dopa-responsive symptoms of tremor, rigidity, and bradykinesia. All these subscales demonstrated a statistically significant improvement for rasagiline and entacapone compared to placebo. The UPDRS dyskinesia subscale did not demonstrate a significant increase when patients were receiving either active treatment compared to placebo. The frequency of dopaminergic adverse events reported with rasagiline was similar to that recorded with the placebo and entacapone groups. Serious adverse events occurred in 41 patients (12 for rasagiline, 12 for entacapone and 17 for placebo). Most commonly reported were nausea, dizziness and dyskinesias.
Schwid et al[15] (PRESTO) Rasagiline 1 or 0.5 mg daily vs placebo	DB, MC, PC, PG, RCT Patients ≥30 years of age who have the presence of at least 2 of the cardinal signs of Parkinson's disease and whose disease severity was not greater than Hoehn and Yahr stage III	N=472 26 weeks	Primary: The change from baseline in mean total daily off time as measured by home diaries, averaged during the treatment period (from 6 weeks, 14 weeks and 26 weeks) Secondary: Change from baseline in CGI-I scores, UPDRS-ADL scores, UPDRS-motor subscale during on	Primary: During the treatment period, the mean adjusted total daily off-time decreased from baseline by 1.85 hours (29%) in patients treated with 1.0 mg/daily of rasagiline, 1.41 hours (23%) in patient treated with 0.5 mg /daily rasagiline and 0.91 (15%) of the placebo-treated patients. The off-time per day was significantly less with rasagiline 1.0 mg/daily by 0.94 hours compared to placebo (95% CI, 0.51 to 1.36 hours; *P*<0.001) and by 0.49 hours for the rasagiline 0.5 mg/daily group compared to placebo (95% CI, 0.08 to 0.91 hours; *P*=0.02). Changes from baseline and the differences between groups were sustained throughout the treatment period. Secondary: Compared to placebo, rasagiline 1.0 and 0.5 mg/daily had statistically significant changes from baseline in the CGI-I scale (*P*<0.001 and *P*=0.003, respectively), the UPDRS-ADL score (*P*=0.004 and *P*=0.008, respectively), the UPDRS motor performance scale (*P*=0.001 and *P*<0.001, respectively) compared to placebo. The PDQUALIF summary scale showed trend towards improvement compared to placebo for the rasagiline 0.5 mg/daily group (*P*=0.07) but not for the rasagiline 1.0 mg/daily group (*P*=0.22). Results did not demonstrate statistical significance.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			periods and the PDQUALIF scale scores Exploratory endpoints: Changes from baseline in the mean total daily on time, the Schwab-England ADL scale during on and off periods and the UPDRS-ADL subscale during on periods	There were statistically significant increases in the mean duration of on time per day during treatment with both dosages of rasagiline, which corresponds to decrease in off time. The rasagiline 1.0 mg/daily group demonstrated statistically significant improvement in the Schwab-England ADL scale during off-time (*P*=0.02) compared to placebo while the rasagiline 0.5 mg/daily group did not demonstrate statistical significance compared to placebo (*P*=0.46). Both treatment-groups did not demonstrate statistically significant differences compared to placebo in the Schwab and England ADL scores during on-time compared to placebo (*P*=0.46 and *P*=0.25 for rasagiline 1.0 and 0.5 mg/daily, respectively). In a post hoc analysis of UPDRS sub scores during on-time, statistically significant improvements in rigidity, bradykinesia and tremor was demonstrated in patients treated with 1.0 mg/daily of rasagiline compared to placebo (*P*=0.02, *P*=0.049 and *P*=0.002, respectively). Rasagiline 0.5 mg/daily demonstrated a significant improvement compared to placebo in UPDRS subscales for postural instability/gait as well as tremor (*P*=0.04 and *P*<0.001, respectively). The number of patients that discontinued treatment due to an adverse event was not statistically significant between the treatment groups and placebo. The adverse event reported by placebo treated patients was 87%, 91% for rasagiline 0.5 mg/daily treated patients and 95% for rasagiline 1.0 mg/daily treated patients. The most commonly reported adverse events were weight loss, vomiting, anorexia and balance difficulty, which occurred more often in the treatment groups compared to placebo.
Siderowf et al[16] (TEMPO) Rasagiline 1 or 2 mg daily vs placebo	DB, MC, PC, PG, RCT Patients ≥35 years old diagnosed with idiopathic Parkinson's disease, had a Hoehn and Yahr	N=404 26 weeks 1-week escalation period followed by 25-week	Primary: Change in total UPDRS scale between baseline and the week 26 visit. Secondary: Changes in the	Primary: Both active treatment groups demonstrated significant benefit compared to the placebo group in the change of total UPDRS score at week 26 from baseline (*P*<0.001 for each comparison). Secondary: 16.7% of the placebo-treated patients reached the secondary end point of needing levodopa therapy, compared with 11.2% of the rasagiline 1 mg-treated patients and 16.7% of the rasagiline 2 mg-treated patients (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	disease severity of less than stage III, not receiving any antiparkinson drugs; required washout was 60 days for selegiline and 14 days for other antiparkinson medications	maintenance period	mental ADL, motor subscale scores (tremor, rigidity, bradykinesia and postural instability/gait disorder), Hoehn and Yahr stage, Schwab-England ADL scale, Beck Depression Inventory score, timed motor tests and the PDQUALIF scale	There was no statistically significant difference in the Kaplan-Meier analysis in the time to need for additional therapy among the three groups (*P* value not reported). Both active treatment groups showed significant improvements in PDQUALIF scores compared to the placebo group (*P* value not reported). All other secondary measures evaluated in the trial did not demonstrate statistical significance when comparing the treatment group to the placebo group. Adverse events were similar in the rasagiline-treatment groups as compared to placebo group. The most commonly observed adverse event were infections (16%) and headache (12%). There were no other adverse events that occurred greater than 10% in the study groups.
Stern et al[17] Rasagiline 1, 2, or 4 mg daily vs placebo	DB, MC, PC, PG, RCT Patients between 40 and 75 years of age who had a primary diagnosis of idiopathic Parkinson's disease and had a Hoehn and Yahr disease severity less than stage III	N=56 10 weeks	Primary: Safety and tolerability Secondary: Efficacy by the changes of the UPDRS scores from baseline CGI-C scale, modified Hoehn and Yahr stage, Schwab and England-ADL scale, and the Beck Depression Inventory	Primary: No serious adverse events were reported in each treatment group. The frequency of adverse events reported by patients receiving rasagiline were similar to those reported by patients receiving placebo. The most commonly reported adverse event in the rasagiline-treated group was pain, headache and dizziness. Secondary: The mean change in the total UPDRS scores in the rasagiline 2 mg group was statistically significant at week 10 from baseline compared to placebo (*P*<0.05). However, patients receiving rasagiline 1 and 4 mg did not show statistically significant changes from baseline compared to placebo. No evidence of drug effect was noted with respect to the CGI-I scale, Hoehn and Yahr stage, Schwab and England-ADL scale or the Beck Depression Inventory. In a responder analysis, 28% of patients receiving rasagiline had an improvement of greater than 30% in total UPDRS scores compared to 0% of patients receiving placebo (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Major Depression Disorder				
Bodkin et al[18] STS 6 mg/daily vs placebo	DB, FD, MC, PC, PG, RCT Men and women 18 to 65 years of age, who met the DSM-IV criteria for MDD with history of a single episode or recurrent episodes were enrolled	N=176 7 weeks total 1 week placebo run-in phase, followed by 6-weeks randomization	Primary: Changes at week 6 from baseline in the HAM-D_{17} scale, HAM-D_{28} scale, MADRS and the CGI-I severity of illness and improvement measure Secondary: Not reported	Primary: STS-treated patients demonstrated statistically significant changes at week 6 from baseline on all clinical measures. Compared to placebo, the STS-treated group showed 46% improvement in HAM-D_{17} (*P*=0.01), 52% improvement in HAM-D_{28} (*P*=0.004) and 79% improvement on the MADRS scale (*P*=0.005). CGI ratings showed significantly less severity of illness and greater global improvement in the selegiline group than in the placebo group (*P*=0.007). Selegiline was very well tolerated in which only 4.5 % of patients treated with selegiline and 5.6% of the patients treated with placebo discontinued therapy due to adverse events. The most significant adverse reaction was application site reactions that most commonly occurred in the selegiline group compared to the placebo group (32 patients vs 15 patients, respectively; *P* value not reported). Secondary: Not reported
Feiger et al[19] STS 6 to 12 mg/daily vs placebo	DB, FD, PC, RCT, TT Men and women, 18 years of age and older who met the DSM-IV criteria for MDD with single or recurrent, moderate to severe disease were enrolled	N=265 8 weeks	Primary: Mean change at week 8 from baseline on the HAM-D_{28} scale, MADRS, and the IDS-SR scale Secondary: Mean change from baseline on the HAM-D_{17} scale, and the core depression symptoms subscale (HAM-D 6-item Bech)	Primary: Patients in the STS-treatment group demonstrated statistically significant improvement compared to placebo in the HAM-D_{28} (*P*=0.03), MADRS (*P*=0.02) and the IDS-SR (*P*=0.03) depression rating scales. The mean improvement from baseline in the HAM-D_{17} score was greater in the STS-treatment group than with the placebo-treatment group (-8.7 vs -7.4, respectively; *P*=0.13). There was a statistically significant difference between the STS-treatment group compared to placebo in the HAM-D (6-item Bech) score at week 8 from baseline (-5.5 vs -4.1, respectively; *P*<0.01). Adverse events were similar in patients receiving STS compared to those receiving placebo. Nine patients treated with STS- and three patients treated with placebo-discontinued treatment due to an adverse event. Treatment related adverse events for the STS group were application site reaction, insomnia, infection, dizziness, dry mouth, nervousness and diarrhea. Highest percentage of adverse reactions for the STS group compared to placebo was for the application site reaction (40% vs 20%, respectively) and insomnia (30% vs 14%, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Amsterdam et al[20] STS 6 mg /daily vs placebo	DB, PC, RCT Men and women ≥18 years of age that met the DSM-IV criteria for MDD with single or recurrent episodes and scored ≥20 on the HAM-D_{17} depression scale	N=289 9 weeks total 1 week single-blind placebo run-in phase, followed by 8-weeks randomization	Primary: Change at week 8 from baseline on the HAM-D_{17}, HAM-D_{28}, MADRS depression rating scales Secondary: Changes from baseline in the CGI-S, CGI-C score, the distribution of HAM-D item 1, Item 3 (depressed mood and suicide) and the percentage of patients with ≥50% reduction in baseline HAM-D_{17}, HAM-D_{28} score	Primary: Patients in the STS-treatment group demonstrated statistically significant improvement compared to placebo in the HAM-D_{28} (P=0.039) and the MADRS (P=0.001) depression rating scales. Patients receiving STS did not demonstrate a statistical significant difference at week 8 from baseline on the HAM-D_{17} scale compared to patients receiving placebo. Secondary: There was no statistically significant difference demonstrated in the CGI-S and CGI-C scores for the STS group compared to the placebo group (P=0.055 and P=0.157, respectively) from baseline. The percentage of patients with the final HAM-D item 3 score of "0" in the STS-treatment group was significantly greater compared to the placebo group (P=0.021) and a non-significant trend favoring STS treatment in the HAM-D item 1 compared to placebo was demonstrated (P<0.07). Statistical significance was not demonstrated for the percentage of patients with ≥50% reduction in baseline HAM-D_{17}, HAM-D_{28} scores in the patients treated with STS compared to placebo. Adverse events were similar in both the treatment group and placebo. Ten STS-treated patients and eight placebo-treated patients discontinued therapy due to adverse events. The only significant difference observed was in the frequency of patch application site reactions (31.5% for the STS group and 15.1% for the placebo group).
Amsterdam et al[21] STS 6 mg/daily vs placebo	DB, MC, PC, PG, RCT Males and females, 18 years and older with a DMS IV diagnosis of MDD and a minimum HAM-D_{17} score of ≥18	N=342 open-labeled phase N=322 double-blind phase 52 weeks	Primary: Comparative proportion of patients in each group studied who met the protocol defined relapse criteria during the double-blind phase	Primary: Significantly fewer patients treated with STS had experienced relapse by week 52 compared to those given placebo (16.8% vs 30.7%; P=0.0025). Secondary: The percentage of patients that responded during the open labeled phase was 53%. Overall mean decreases from baseline on the HAM-D_{17}, HAM-D_{28}, and the MDRS scores were -16.3 (69% improvement), -21.8 (71% improvement) and -21.1 (71% improvement), respectively, for study week 10 completers.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Secondary: Percentage of patients responding during the 10-week open label phase, the proportion of patients in each group who relapsed by study week 26 of the double-blind phase, the cumulative rate of relapse at study weeks 26 and 52, and the time to relapse	Significantly fewer patients treated with STS had experienced relapse by week 25 compared to those given placebo (16.8% vs 29.4%; *P*=0.0051). The cumulative rates of relapse were significantly lower in the patients treated with STS compared to those given placebo at week 26 (20% vs 37%; *P*=0.0115) and at week 52 (20% vs 39%; *P*=0.0061). The time to relapse was significantly longer in the STS-treated group compared with the placebo group (*P*=0.0048).

Drug regimen abbreviations: ODT=orally disintegrating tablet, STS=selegiline transdermal system
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double-dummy, FD=fixed dose, MA=meta-analysis, MC=multicenter, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial, TT=titrating trial
Miscellaneous abbreviations: ADL=activities of daily living, CGI-I=Clinical Global Impressions-Improvement scale, CGI-S=Clinical Global Impression-Severity, DMS-IV=Diagnostic and Statistical Manual of Mental Disorders, HAMD=Hamilton Rating Scale for Depression, IDS-SR=Inventory of Depressive Symptomatology Self-report, MADRS= Montgomery Asberg Depression Rating Scale, MAO-B=Monoamine Oxidase-B, MDD=major depressive disorder, ODT=orally disintegrating tablet, PDQUALIF=Parkinson's Disease Quality of Life Scale, PGI-I=Patient Global Impression Improvement, UPDRS=Unified Parkinson's Disease Rating Scale

Special Populations

Table 5. Special Populations[2-7]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal dysfunction	Hepatic dysfunction	Pregnancy Category	Excreted in Breast Milk
Rasagiline	Safety and efficacy not established in pediatric patients. No dose adjustment required in elderly patients.	No dose adjustment required in patients with mild renal impairment.	Patients with mild impairment should be given 0.5 mg/day; should not be used in patients with moderate/ severe impairment.	C	Unknown; use with caution when administering to nursing women.
Selegiline	Safety and efficacy not established in pediatric patients. Increased risk of orthostatic hypotension and dizziness in patients over the age of 65. The effect of age on the pharmacokinetics or metabolism of selegiline transdermal patch has not been evaluated.	Unknown; use with caution in patients with renal impairment. No dosage adjustment of selegiline transdermal patch is required in patients with renal function impairment.	Unknown; use with caution in patients with hepatic impairment. No dosage adjustment of selegiline transdermal patch is required in patients with moderate hepatic function impairment.	C	Unknown; use with caution when administering to nursing women.

Adverse Drug Events

Table 6. Adverse Drug Events[2-7]

Adverse Event	Rasagiline (Azilect®) (%) reported	Selegiline (Eldepryl®) (%) reported	Selegiline disintegrating tablets (Zelapar®) (%) reported	Selegiline transdermal patch (EMSAM®) (%) reported
Cardiovascular System				
Hypertension	-	✔	3	✔
Palpitations	-	2	-	-
Digestive System				
Anorexia	-	-	-	✔
Constipation	-	✔	4	✔
Diarrhea	✔	2	2	9
Dyspepsia	7	-	5	4
Dysphagia	-	✔	2	-
Flatulence	-	-	2	✔
Gastroenteritis	3	✔	✔	✔
Nausea	-	20	11	-
Stomatitis	-	-	5	-

Adverse Event	Rasagiline (Azilect®) (%) reported	Selegiline (Eldepryl®) (%) reported	Selegiline disintegrating tablets (Zelapar®) (%) reported	Selegiline transdermal patch (EMSAM®) (%) reported
Tooth disorder	-	-	2	-
Vomiting	✔	✔	3	✔
Hemic and Lymphatic System				
Ecchymosis	2	-	2	✔
Metabolic and Nutritional Disorders				
Hypokalemia	-	✔	2	-
Peripheral edema	-	-	-	✔
Musculoskeletal System				
Arthralgia	7	-	✔	✔
Arthritis	2	-	✔	-
Leg cramps	-	✔	3	-
Myalgia	-	-	3	-
Pathologic fracture	-	-	-	✔
Nervous System				
Agitation	-	-	-	✔
Anxiety/tension	-	2	✔	-
Ataxia	-	-	3	-
Confusion	-	6	-	-
Depression	5	✔	2	-
Dizziness	✔	14	11	-
Dreams (vivid)	-	4	✔	-
Dry Mouth	-	6	4	8
Dyskinesia	-	4	6	-
Fall	5	✔	-	-
Hallucinations	✔	6	4	-
Headache	14	4	7	18
Insomnia	-	2	7	12
Lethargy	-	2	-	-
Malaise	2	✔	-	-
Paresthesia	2	-	✔	✔
Somnolence	-	-	3	-
Thinking abnormal	-	-	-	✔
Tremor	-	✔	3	-
Vertigo	2	✔	✔	-
Respiratory System				
Cough	-	-	-	✔
Bronchitis	-	-	-	✔
Dyspnea	-	✔	3	-
Pharyngitis	-	-	4	3
Sinusitis	-	-	-	3
Rhinitis	3	-	7	-
Sexual Dysfunction				
Abnormal ejaculation	-	-	-	1
Anorgasmia	-	-	-	0.2
Decreased libido (men)	-	-	-	0.7
Impotence	-	-	-	0.7
Skin and Appendages				
Acne	-	-	-	✔

Adverse Event	Rasagiline (Azilect®) (%) reported	Selegiline (Eldepryl®) (%) reported	Selegiline disintegrating tablets (Zelapar®) (%) reported	Selegiline transdermal patch (EMSAM®) (%) reported
Application site reaction	-	-	-	24
Rash	✔	✔	4	4
Skin disorders	✔	✔	6	-
Sweating	-	-	-	✔
Urinary System				
Dysmenorrhea	-	-	-	✔
Metrorrhagia	-	-	-	✔
Urinary retention	-	2	✔	-
Urinary tract infection	-	-	-	✔
Other				
Abdominal pain	-	8	-	-
Back pain	-	2	5	-
Chest pain	-	-	2	✔
Conjunctivitis	3	-	-	-
Fever	3	-	✔	-
Flu syndrome	5	-	-	-
Leg pain	-	2	-	-
Neck pain	2	-	-	✔
Pain	-	2	8	-
Weight gain	-	-	-	2.1
Weight loss	-	2	-	5

✔ % Not specified.

-Event not reported.

Contraindications / Precautions[2-7]

Monoamine oxidase (MAO) inhibitors are contraindicated in patients who have a known hypersensitivity to any formulation of selegiline or rasagiline. These agents are also contraindicated for use with meperidine due to reports of patients experiencing coma, severe hypertension/hypotension, severe respiratory depression, convulsions, malignant hyperpyrexia, excitation, peripheral vascular collapse and death. MAO inhibitors are contraindicated for use with sympathomimetic amines including amphetamines, cold products and weight-reducing preparations that contain vasoconstrictors (e.g., pseudoephedrine, phenylephrine, phenylpropanolamine and ephedrine). Severe hypertensive reactions have followed the administrations of sympathomimetics and non-selective MAO inhibitors. MAO inhibitors should not be administered along with other MAO-inhibitors (selective or non-selective) due to an increased risk of non-selective MAO inhibition that may lead to a hypertensive crisis. Fourteen days should elapse between discontinuation of selegiline/rasagiline and initiation of another MAO inhibitor.

Drug Interactions

Table 7. Drug Interactions[2-7]

Name	Interacting Medication or Disease	Potential Result
Monoamine oxidase-B Inhibitors (MAO-B) inhibitors	Carbidopa/levodopa	May result in exacerbation of levodopa adverse effects, requiring a reduction in levodopa dosage.
MAO-B inhibitors	CYPP450 enzyme inhibitors and inducers	CYP2B6 and CYP3A4 are involved in the metabolism of MAO-B inhibitors; use with caution. CYP2A6 may have a minor role in the metabolism.

Name	Interacting Medication or Disease	Potential Result
MAO-B inhibitors	Dextromethorphan	May cause brief episodes of psychosis or bizarre behavior.
MAO-B inhibitors	MAO inhibitors	Increased risk of non-selective MAO inhibition that may lead to a hypertensive crisis.
MAO-B inhibitors	Meperidine	Occurrence of stupor, muscular rigidity, severe agitation, elevated temperature, hallucinations, or even death.
MAO-B inhibitors	Selective serotonin reuptake inhibitors	May cause severe toxicity and serotonin-syndrome.
MAO-B inhibitors	Sympathomimetic medications (ephedrine)	May cause severe hypertensive reactions.
MAO-B inhibitors	Tricyclic and tetracyclic antidepressants	May cause severe toxicity and serotonin-syndrome.
Rasagiline	CYP1A2 Inhibitors (ciprofloxacin)	Drug concentration may increase up to two-fold with concurrent ciprofloxacin use and other CYP1A2 inhibitors.

Dosage and Administration

Table 8. Dosing and Administration[2-7]

Generic Name	Adult Dose	Pediatric Dose	Availability
Rasagiline	Parkinson's disease: Tablet: initial monotherapy, 1 mg once daily; initial adjunctive to levodopa/carbidopa, 0.5 mg once daily; maintenance, 0.5 to 1 mg once daily	Safety and efficacy in children have not been established.	Tablet: 0.5 mg 1 mg
Selegiline	Parkinson's disease: Tablet: initial and maintenance, 5 mg twice daily; maximum, 10 mg daily Orally disintegrating tablet: initial, 1.25 mg daily for 6 weeks; maintenance, 2.5 mg daily; maximum, 2.5 mg daily Depression: Transdermal system: initial, 6 mg/24 hours patch topically every 24 hours; maintenance, 6 mg/24 hours topically every 24 hour, may increase at increments of 3 mg/24 hours every two weeks up to 12 mg/24 hours; maximum, 12 mg/24 hours topically daily	Safety and efficacy in children have not been established.	Capsule*: 5 mg Orally disintegrating tablet: 1.25 mg Tablet†: 5 mg Transdermal patch: 6 mg/24 hours 9 mg/24 hours 12 mg/24 hours

*Capsule available as brand and generic.
†Tablet is only available as generic (brand no longer available).

Clinical Guidelines

According to the National Institute for Health and Clinical Excellence (NICE) there is no universal first-choice therapy for patients with Parkinson's disease.[8] Levodopa, dopamine agonists and monoamine oxidase-B (MAO-B) inhibitors may all be used in patients with early Parkinson's disease for symptomatic treatment. The MAO-B inhibitors are considered more convenient compared to the other agents due to ease of administration and may be considered in patients who need symptomatic treatment prior to the administration of dopaminergic therapy. Anticholinergics should be limited to younger patients with early Parkinson's disease associated with severe tremor. In elderly patients, early use of levodopa is recommended, as they are less prone to developing motor complications but more sensitive to neuropsychiatric adverse events.

In addition, there is no single agent of choice for late stage Parkinson's disease.[8] Levodopa, dopamine agonists, MAO-B inhibitors and catechol-O-methyl transferase (COMT) inhibitors may all be considered to reduce motor fluctuations in patients with late stage Parkinson's disease. For the symptomatic control of wearing-off in late, complicated Parkinson's disease, several strategies have been recommended. Such strategies include increasing the dosing frequency of levodopa or switching to a controlled-release formulation of the medication. Also adding a COMT-inhibitor, MAO-B inhibitor or dopamine agonist as adjunctive therapy is also recommended. If these strategies fail it is recommended that amantadine or an anticholinergic be considered. For the symptomatic control of dyskinesias in late, complicated Parkinson's disease the addition of amantadine is recommended. Other strategies include reducing the dose size of levodopa or discontinuing or reducing the dose of MAO-B inhibitors or COMT inhibitors, however these strategies increase the risk of worsening off time.

Table 9. Clinical Guidelines

Clinical Guideline	Recommendations
National Institute for Health and Clinical Excellence (NICE): **Parkinson's Disease: Diagnosis and Management in Primary and Secondary Care (2006)[8]**	• There is no universal first-choice therapy for patients with Parkinson disease (PD). Clinical and lifestyle characteristics of the patient should be taken into account. • Levodopa may be used in patients with early PD for symptomatic treatment with doses kept as low as possible to reduce the development of motor complications. • Dopamine agonists may be used in patients with early PD for symptomatic treatment. Dopamine agonists should be titrated to a clinically efficacious dose and another agent in the class maybe used if the patient fails therapy or side effects prevents titration. • Monoamine oxidase-B (MAO-B) inhibitors may be used in patients with early PD for symptomatic treatment. • Beta-blockers may be used for symptomatic treatment of selected people with postural tremor, but are not considered first-line agents. • Amantadine may be used in patients with early PD, but is not considered a first-line agent. • Anticholinergics may be used in young patients with early PD for symptomatic treatment associated with severe tremor. These agents are not considered first-line due to limited efficacy and the propensity to cause neuropsychiatric side effects. • Extended-release levodopa should not be used to delay the onset of motor complications in patients with early PD. • Most patients with PD will develop motor complications over time and will require levodopa therapy. Adjuvant medications have been developed to take concomitantly with levodopa to help reduce the motor complications and improve quality of life associated with late stage PD. • There is no single agent of choice for late stage PD. • Extended-release levodopa may help reduce motor complications in

Clinical Guideline	Recommendations
	patients with late stage PD, but is not considered a first-line agent. • Dopamine agonists may be used to reduce motor fluctuations in patients with late stage PD. Dopamine agonists should be titrated to a clinically efficacious dose and another agent in the class maybe used if side effects prevent titration. • MAO-B inhibitors may be used to reduce motor fluctuations in patients with late stage PD. • Catechol-O-methyl transferase (COMT) inhibitors may be used to reduce motor fluctuations in patients with late stage PD. This class of medication is taken concomitantly with levodopa. • Amantadine may be used to reduce dyskinesias in patients with late stage PD. • "Drug holidays" should be avoided because of the risk of developing neuroleptic malignant syndrome.
American Academy of Neurology (AAN) Practice Parameter: **Initiation of Treatment for Parkinson's Disease: An Evidence Based Review (2002)**[9]	• Patients with PD, who require symptomatic treatment, may be started with selegiline prior to the administration of dopaminergic therapy. • Selegiline has mild symptomatic benefits in PD, and no convincing evidence of neuroprotective benefits. • Levodopa, cabergoline, ropinirole and pramipexole are effective in ameliorating motor complications and impairment in the activities of daily living (ADL) in patients with PD who require dopaminergic therapy. Of these agents, levodopa is more effective in treating motor complications and ADL disability and is associated with a higher incidence of dyskinesias than dopamine agonists. • Levodopa or a dopamine agonist may be initiated in patients with PD who require dopaminergic therapy. • Cabergoline, ropinirole and pramipexole resulted in fewer motor complications (i.e., wearing off, dyskinesias, on-off fluctuations) compared to levodopa. • Treatment with a dopamine agonist was associated with more frequent adverse drug reactions (hallucinations, somnolence and edema in the lower extremities) than levodopa. • When initiating treatment with levodopa in patients with PD, either an immediate-release or sustained-release formulation may be used. In clinical trials, there was no difference in the rate of motor complications between the two formulations.
AAN Practice Parameter: **Treatment of Parkinson's Disease with Motor Fluctuations and Dyskinesia (2006)**[10]	• Rasagiline and entacapone demonstrated statistically significant reduction in off time as compared to placebo in clinical trials. It is recommended that these two agents should be offered to reduce off time. • Pergolide demonstrated some improvement in the reduction in off time as compared to placebo in clinical trials. However, a large number of patients on pergolide experienced more dyskinesias. Pramipexole demonstrated some reduction in off time in placebo controlled trials. Ropinirole and tolcapone showed reduction in off time compared to placebo. It is recommended that pergolide, pramipexole, ropinirole and tolcapone can be considered to reduce off time. Due to side effects and the strength of the studies, entacapone and rasagiline are preferred over pergolide, pramipexole, ropinirole and tolcapone. • Apomorphine, cabergoline and selegiline were studied in clinical trials that lacked proper enrollment and methods to provide conclusive evidence of reducing off time. It is recommended that these agents may be considered to reduce off time.

Clinical Guideline	Recommendations
	• Bromocriptine and extended-release carbidopa/levodopa do not help to reduce off time. • Amantadine demonstrated reduction in dyskinesia compared to placebo in clinical trials. It is recommended that amantadine may be considered for patients with PD for reducing dyskinesias. • Deep brain stimulation of the subthalamic nucleus may be considered as a treatment option in PD patients to help improve motor function and to reduce motor fluctuations, dyskinesias and medication usage.
European Journal of Neurology: **Joint Task Force Report: European Federation of Neurological Societies/Movement Disorder Society; Early (Uncomplicated) Parkinson's Disease (2006)**[11]	• No adequate clinical trials have been conducted to provide definitive evidence for pharmacological neuroprotection. • In the management of early PD, MAO-B inhibitors have a modest benefit in treating the symptomatic complications of PD compared to levodopa and dopamine agonists. These agents are more convenient due to the ease of administration (i.e., one dose, once daily, no titration). • Amantadine and anticholinergics offer minimal symptom control compared to levodopa. • Anticholinergics are poorly tolerated in the elderly and use should be restricted to younger patients. • Levodopa is the most effective anti-Parkinson's drug for symptomatic relief. • Early use of levodopa in the elderly is recommended, as they are less prone to developing motor complications but more sensitive to neuropsychiatric adverse events. • Pramipexole and ropinirole are effective dopamine agonists as monotherapy in the treatment of early stage PD. • Convincing evidence that older agents in the class are less effective than the newer non-ergot agents is lacking. • Dopamine agonists have a lower risk of developing motor complications than compared to levodopa. These agents do have a greater incidence of adverse effects, which include hallucinations, somnolence and edema in the lower extremities. • Younger patients should be started on a dopamine agonist as initial treatment to prolong the use of levodopa and the development of motor complications.
European Journal of Neurology: **Joint Task Force Report: European Federation of Neurological Societies/Movement Disorder Society; Late (Complicated) Parkinson's Disease (2006)**[12]	<u>Symptomatic Control of Wearing-off</u> • Adjusting the levodopa dose by increasing the dosing frequency has been beneficial to control off time. • Switching from the standard formulation of levodopa to the controlled-release formulation improves wearing-off symptoms. • Adding a COMT-inhibitor or a MAO-B inhibitor is effective in reducing off time by 1-1.5 hours/day. • Adding a dopamine agonist provides modest benefit. All dopamine agonists are equally effective and efficacious in reducing off time. Pergolide and other ergot derivatives are reserved for second-line use, due to the adverse effect of valvulopathy. • Addition of amantadine or anticholinergics should be considered in patients with severe off symptoms who fail the recommended strategies listed above. <u>Symptomatic Control of Dyskinesias</u> • Patients may benefit for up to 8 months by adding amantadine 200-

Clinical Guideline	Recommendations
	400 mg/day for the treatment of dyskinesias. • Reducing the dose size of levodopa has been beneficial in reducing dyskinesias. The risk of off-time increases but can be compensated by increasing the frequency of levodopa dosing. • Discontinuing or reducing the dose of MAO-B inhibitors or COMT inhibitors can help control dyskinesias, however the risk of worsening off-time increases. • The addition of clozapine or quetiapine has shown to be beneficial in reducing peak dose dyskinesia. Clozapine's adverse effect of agranulocytosis limits its use. • Deep brain stimulation of the subthalamic nucleus allows the reduction of dopaminergic treatment. • Apomorphine given as a continuous subcutaneous infusion under direct medical supervision allows for the reduction of levodopa therapy and helps control dyskinesias.

Conclusions

Monoamine oxidase-B Inhibitors (MAO-B) inhibitors are used for the treatment of early Parkinson's disease. Based on clinical trials and guidelines, these agents are potentially beneficial for patients diagnosed with early Parkinson's disease. According to national and international treatment guidelines, MAO-B inhibitors may be used in patients with early Parkinson's disease for symptomatic treatment and are considered to have modest benefit compared to levodopa and dopamine agonists.[8-12]

Some of the MAO-B inhibitors allow for once daily dosing without titration. Rasagiline has evidence suggesting it helps reduce the off time associated with levodopa use, which is usually inevitable for most Parkinson's disease patients. Overall MAO-B inhibitors have demonstrated the potential to delay the need for levodopa therapy by 4 to 8 months, potentially delaying the onset of levodopa induced motor complications.[1] MAO-B inhibitors may help treat wearing off effects of patients with late stage Parkinson's disease with severe motor complication on levodopa therapy.[8-12] Currently, there is no universal first-choice therapy for patients with late stage Parkinson's disease on levodopa therapy, and for these patients, clinical/lifestyle characteristics of the patient should be taken into account before the initiation of therapy.[8]

Recommendations

In recognition of the well-established role of monoamine oxidase-B Inhibitors (MAO-B) inhibitors in the treatment of Parkinson's disease and cost considerations, no changes are recommended to the current approval criteria.

Generic selegiline is preferred on The Office of Vermont Health Access (OVHA) preferred drug list.

Azilect® (rasagiline), Eldepryl® (selegiline) and Zelapar® (selegiline ODT) require prior authorization with the following approval criteria:

Eldepryl® requires prior authorization with the following approval criteria:
- The patient has had a documented intolerance to the generic product.

Azilect® requires prior authorization with the following approval criteria:
- The diagnosis or indication is Parkinson's disease.

AND
- The patient has had a documented side effect, allergy, or treatment failure with selegiline.

AND
- The dose requested does not exceed 1 mg/day

Zelapar® requires prior authorization with the following approval criteria:
- The diagnosis or indication is Parkinson's disease.

AND
- The patient is on current therapy with levodopa/carbidopa.

AND
- Medical necessity for disintegrating tablet administration is provided (i.e. inability to swallow tablets or drug interaction with oral selegiline).

AND
- The dose requested does not exceed 2.5 mg/day.

Emsam® requires prior authorization with the following approval criteria:
- The patient has had a documented side effect, allergy, or treatment failure with at least 3 antidepressants from 2 of the major antidepressant classes (Miscellaneous, SNRIs, SSRIs, Tricyclic Antidepressants).

OR
- The patient is unable to tolerate oral medications.

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